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Topical Anaesthesia for Prompt and Prolonged Wound Pain Relief: Lessons from Wide Scale Use on Major Open Wounds in Livestock - An Editorial

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ABSTRACT

Wounds are painful, particularly if they require debridement or suture. Systemic analgesics or injected local anaesthesia can be insufficient, unavailable and/or painful to administer. It would be ideal to have a topical anaesthetic product that could be promptly applied to any wound, regardless of its size or type, to immediately numb it, alleviate pain with prolonged effect, and provide sufficient anaesthesia to allow for debridement or suturing without the need for painful injected local anaesthetics. At present, however, aside from products used on minor cuts, there are few, if any topical anaesthetic products registered and approved (i.e., of proven safety and efficacy) for use on open wounds of this nature in humans. More-over, needed safety and efficacy data to support such applications are lacking. This is not the case in veterinary medicine however, where a combination topical anaesthetic and antiseptic solution formulated specifically for such use, has been developed, approved and is now extensively used for such indications. This is as a consequence of a 20-year research and development programme focused on developing a practical, yet safe and effective method of providing pain relief for livestock undergoing surgical husbandry procedures in Australia. These procedures, (such as castration, tail docking, dehorning and Mulesing), performed 'in the field' by farmers using a swift technique, leave painful open wounds that heal by secondary intention. Traditional pain relief methods were impractical, prompting us to explore topical anaesthesia. Trials led, in outcome, to the development of a formulation which combines rapid onset and long-acting local anaesthetics (lidocaine and bupivacaine), with a vasoconstrictor (adrenaline) and an antiseptic (cetrimide), in a viscous biocompatible base capable of being sprayed onto the wound and remining in place. Positive safety and efficacy data have supported multiple product registrations including to mitigate pain associated with castration wounds in sheep, cattle, and pigs; Mulesing and tail-docking wounds in lambs; scoop and cautery (burn) dehorning wounds in calves; infectious hoof and mouth ulcers in cattle. Six-7 million animals are now treated annually, with over 120 million animals treated to date. This editorial reviews data from this development programme, discusses new findings, and explores potential human applications.

Introduction

Open wounds can cause significant pain and suffering. Although topical anaesthesia can be effective to mitigate pain, there are few if any such products specifically formulated and approved for such use in humans, particularly if wounds are large or of high vascularity. This is not so in veterinary medicine, however. Over the past 20 years, there has been a significant advance in this field due to the advent of Tri-Solfen® (Animal Ethics Pty Ltd, Vic Australia), a topical local anaesthetic formulation designed to be able to be sprayed or instilled directly onto open wounds and stay there, to numb the wound and provide quick and lasting pain relief. This includes wounds of large surface area and/ or compound tissue type. Insights from the development and use of this formulation in animals are now informing phase 2 trials investigating analogous uses in humans. This editorial, reviews the development of Tri-Solfen, discusses new findings, and explores potential human applications.

Topical wound anaesthesia in veterinary medicine

A major advance in the use of topical wound anaesthesia in veterinary medicine was initiated in 2004 in Australia, driven by the need to address pain in livestock caused by surgical husbandry procedures, including castration, tail-docking, Mulesing, and dehorning. These procedures, performed on infant animals for health and welfare or production reasons, are typically performed on-farm in remote locations, with a swift technique (blade or cautery iron) but without full aseptic technique. They result in a range of contaminated open wound types (skin laceration or degloving wounds, amputation, burn and / or visceral wounds) depending on the procedure, which are left open to heal by secondary intention. At the initiation of the research programme, hundreds of animals were undergoing these these procedures at a time, without analgesia as standard methods of analgesia or anaesthesia were unavailable or impractical for use in this setting. This prompted the exploration of topical wound anaesthesia.

Although topical anaesthesia is widely used in both veterinary and human medicine, this is primarily for use on intact skin or mucous membranes, and / or minor cuts and grazes, for which safety and efficacy profiles are well established[1]. It had not previously been trialled for use on major open wound types of the nature and scale seen following livestock surgical husbandry procedures, however.

Local anaesthetics function by inhibiting conduction in sensory nerve fibres. Administered topically, they must penetrate the skin or mucous membrane to reach sensory nerve fibres located in subdermis. They have limited ability to penetrate keratinised skin, (particularly if covered with wool or fur), limiting their effectiveness for pre-procedural skin anaesthesia in this setting. Conversely, they can readily penetrate mucous membranes, or where the stratum corneum is breached, such as in open wounds, exhibiting onset times within seconds or minutes and demonstrating higher potency[2,3].

Since the livestock husbandry procedures are performed swiftly (in a matter of seconds) we hypothesised that topical anaesthesia applied immediately after the procedure may numb the wound within seconds, rapidly alleviating pain. We further posited that duration of effect may be maximised by including a long-acting local anaesthetic, adrenaline and a delivery base that allowed prolonged contact with the wound. Our objective was to develop an economical “spray and stay” formulation that farmers could apply “in the field” directly onto wounds to deliver rapid-onset analgesia and extended duration of effect, as well as surface wound antisepsis.

A review of the available data suggested that the primary challenge would be to balance local anaesthetic efficacy against the risk of rapid or erratic systemic absorption or development of local anaesthetic systemic toxicity (LAST), and / or possible adverse effects on wound healing.

These considerations led us to trial different anaesthetic combinations and formulations to derive a formulation with an optimal safety and efficacy profile for use on major open wounds of this nature. In outcome, the formula derived, (Tri-Solfen), contains a rapid onset local anaesthetic (lidocaine 5%), a long-acting local anaesthetic (bupivacaine 0.5%), with a vasoconstrictor (adrenalin 1:40,000), along with a surface antiseptic (cetrimide 0.5%). These actives are contained in a biocompatible viscous fluid base capable of being sprayed or instilled directly onto wounds and staying in place, allowing prolonged delivery of actives.

Initial trials were conducted in lambs undergoing routine tail-docking and Mulesing. In Australia, these procedures are performed simultaneously, intended to provide long-term resistance to severe flystrike. They result in a large open wound consisting of an amputated tail stump with full-thickness skin excision over the tail and perineum. Trials confirmed that Tri-Solfen application induced rapid wound anaesthesia within 1 minute and prolonged sensory analgesia up to 24 hours following application, as evidenced by direct sensory testing and observed pain-related behaviour[4,5]. Additional trials, as required by veterinary medicine approval regulations, were completed, including "Target Animal Safety" and "Human Food Safety," trials. These provided data on the safety of using the product in sheep, even in overdose situations, based on haematological, biochemical, and histological parameters, as well as metabolic and pharmacokinetic data from blood, urine, and edible tissues. No adverse or toxic effects were seen, even at doses up to five times the recommended amount with three repeat treatments. Maximum blood concentrations were observed 2 - 4 hours after application and remained below toxic thresholds, despite doses of up to 1.2ml/kg (containing 60mg/kg lidocaine hydrochloride and 6mg/kg bupivacaine hydrochloride). Based on these data, the product was granted emergency permit regulatory approval in 2008, and full registration in 2012[6]. It has since been applied to approximately 6-7 million lambs annually, totalling over 120 million animals, without significant drug-related adverse events reported in pharmacovigilance tracking.

Subsequently, numerous trials have been completed, investigating the safety and efficacy of Tri-Solfen use on different wound types, and in different species. Positive

results have led to regulatory approvals in many regions, with more in progress. In Australia, in addition to Mulesing and tail docking, Tri-Solfen has proven safe and effective, and is now also approved for use to mitigate pain associated with; sheep castration[7], calf castration, dehorning, and disbudding[8,9], piglet castration[10,11,12] and laceration wounds in horses[13]. It is also approved for several of these indications in New Zealand, the United Kingdom, Canada, and Portugal, with wider European approval for piglet castration pending.

The product is typically applied to wounds immediately after procedures, by metered dose spray or instillation sufficient to fully coat the wound including the cut skin edge and wound margin. Typically, 1ml of Tri-Solfen covers a wound area of 4cm^2, requiring doses up to 1 - 1.2ml / kg for animal indications to date. For castration procedures, the formulation is administered during, rather than immediately after the procedure. It is applied following skin incision and extrusion of the testes, but prior to the ligation of the spermatic cords. This ensures that the cut skin edge of the scrotum and the spermatic cords are coated, as pain from traumatised nerve tissue originates from these two locations. Direct application to the spermatic cords in piglets leads to pre-emptive anaesthesia within 30 seconds, allowing for subsequent painless ligation, which is otherwise the most painful part of the procedure[11,12].

Tri-Solfen is also reported to be effective for pre-emptive anaesthesia of hoof abscess wounds in cattle before debridement procedures[14]. As well, it is proven effective to alleviate pain from diffuse ulcerative lesions in cattle with foot and mouth disease, resulting in rapid and lasting improvements in locomotion and feeding. Now granted regulatory approval for such use in several African and Southeast Asian countries, it is providing a new method for managing this debilitating disease[15].

Topical wound anaesthesia, potential human wound applications

There are numerous scenarios in which topical wound anaesthesia, such as this, could be similarly advantageous for alleviating wound pain in humans, particularly where existing options are unavailable, ineffective, or painful to administer. Three potential applications, analogous to approved uses of Tri-Solfen in animals, are:

First: Prompt or immediate use "in the field" for acute traumatic wounds, to rapidly address pain and provide initial antisepsis, such as could be used by first responders, including in war zones, natural disasters, mass trauma events, ambulances, emergency rooms, or medical clinics. There are few, if any such treatments currently available for direct application to wounds to alleviate pain in such situations. Systemic analgesia, such as opioids may be used, and/or injured people must wait until reaching a treatment centre. Opioids can have deleterious side effects and risk dependency. Used alone or as part of multi-modal therapy, topical anaesthesia may reduce the need for opioids and lower these risks[16].

Second: Use to reduce pain from wounds with significant skin denuding or ulceration such as caused by burns, infectious conditions, split skin grafting, radiation, laser treatment or chronic ulceration. These wounds heal slowly by secondary intention and can be very painful due to relatively large areas of exposed nerve fibres. Existing topical anaesthetic creams are approved for use on minor cuts and grazes, however they are not formulated, nor proven to be safe or effective, for use on larger more vascular open wounds of this nature, nor are they formulated for prolonged duration of analgesia.

Third: Use to provide painless pre-emptive wound anaesthesia prior to procedures such as cleaning, debriding and/or suturing wounds. This method could reduce or eliminate the need for painful injected local anaesthesia and contribute to post-procedural pain relief if formulated for prolonged action[17]. Previously, several pharmacy-compounded topical anaesthetic combinations with adrenaline, have been reported as efficacious to provide a painless alternative to injected local anaesthesia for pre-emptive wound anaesthesia prior to suture of small lacerations (< 7-10cm). Early examples contained cocaine (e.g., "TAC" containing tetracaine, adrenaline and cocaine) but more recent ones use lidocaine (e.g., "LAT" consisting of lidocaine 5%, tetracaine 2-5% and adrenaline 1:1-2000), preferred for safety[18]. To date, however, formulations such as these have not undergone formal regulatory trials or approval such that availability is limited by compound prescription rules, and there is lack of required rigorous safety and efficacy data, particularly pertaining to use on larger wounds.

It is not clear what has hindered the development of topical anaesthetic products to meet these needs in the past, however it may relate to concerns over potential safety or lack of efficacy. New data from Tri-Solfen use in animals challenge these concerns, however.

In terms of safety, the principal risk when applying topical anaesthetics to wounds derives from the potential for rapid systemic absorption into the bloodstream, and risk of developing LAST. Symptoms of LAST can be severe encompassing central nervous system symptoms such as diplopia, muscle twitching, and seizures, and cardiovascular symptoms including hypotension, arrhythmias, and cardiovascular collapse[19]. Although unable to readily penetrate keratinised skin, systemic absorption of topically applied local anaesthetics can increase significantly if applied; over large surface areas[20], under occlusive dressings[21], to mucosal tissues[2] or to open wounds, resulting in a heightened risk of LAST. Risks are particularly high when topical anaesthetics are used without adrenaline. For example, maximum drug plasma concentration (Cmax) and area under the drug plasma concentration–time curve values of lidocaine were significantly increased by 448.6% and 161.5%, respectively, following application of EMLA® (a eutectic mixture of local anaesthetics lidocaine and prilocaine 2.5% each, with skin penetration enhancers, Astra Pharmaceuticals Westborough, Massachusetts), to lacerated mouse skin in comparison with intact mouse skin[22], and toxic level absorption has been reported as a consequence of off-label clinical use of EMLA on inflamed skin[23]. Consequently, EMLA is currently approved only for use on intact skin, minor wounds such as small cuts and grazes, or wounds with low vascularity, such as chronic venous ulcers.

The risk of rapid or excessive local anaesthetic absorption following topical or wound application can be reduced, however via co-administration with adrenaline[24]. Applied topically to mucous membranes or open wounds, adrenaline induces significant local vasoconstriction[25]. This counteracts vasodilatory effects of anaesthetics such as lidocaine and bupivacaine, thereby preventing and delaying their systemic absorption[26]. Consistent with this, bupivacaine Cmax was reduced by 50% and time to peak delayed from 15 minutes to 2-4 hours when bupivacaine 0.5% was applied topically to piglet castration wound as Tri-Solfen (with adrenaline) as compared to as 0.5% bupivacaine solution for injection (without adrenaline) (unpublished data). Applied topically to a range of open wounds in cattle, the maximum relative bioavailability of lidocaine and bupivacaine administered as Tri-Solfen, was 25% of that seen when the same dose was administered by subcutaneous injection. Of note, maximum bioavailability was seen following application to relatively vascular wounds including castration wounds and calf disbudding wounds (scalp wounds). There was negligible absorption following application to wounds of low vascularity such as hoof abscess wounds (unpublished data). Hence, consistent with the inclusion of adrenaline 1:40,000 in the formulation, and as confirmed in studies submitted for regulatory approvals and post approval clinical monitoring to date, Tri-Solfen, applied topically to open wounds in livestock does not induce systemic toxicity, even when applied in doses up to 1.2 ml/kg (60mg/kg lidocaine and 6mg/kg bupivacaine) to large, complex or highly vascular wounds of the nature seen following surgical husbandry procedures.

Topical wound application of adrenaline may be beneficial to decrease capillary bleeding. In human medicine it is commonly used for this purpose, including on wounds of large surface area, such as burn surgery wounds. If absorbed into the blood stream, adrenaline is quickly metabolised, but excessive amounts may cause central adrenergic effects, such as tachycardia, hypertension, and arrhythmias. Used on wounds of large surface area in humans, adrenaline concentrations of 1:20,000 - 1:50,000 avoid central adrenergic effects that may be seen with higher concentrations of 1:1,000 - 1:2,000, without compromising haemostatic effect[27]. Absence of evidence of central adrenergic toxicity in animals treated with Tri-Solfen (1:40,000) aligns with these findings.

The potential impact of topical anaesthesia on wound healing is also of concern. Existing data on this topic are conflicting. Negative impacts have been suggested in some *in-vitro* studies[28], while data from *in-vivo* studies have been less convincing[29]. Adverse impacts on wound healing in animals treated with Tri-Solfen have not been observed, other than a transitory reduction in wound contraction rate in the first 7 days following use during neonatal piglet castration. This, however, was quickly caught up, resulting in no overall impact on healing time, histological or clinical parameters (unpublished data). Conversely, the opposite effect, (enhanced early wound contraction), has been reported in Tri-Solfen treated lambs following Mulesing and tail docking[4]. Additionally, studies suggest that the prompt application of antiseptic to contaminated wounds, such as occurs with Tri-Solfen application, may also be beneficial[30]. In humans, lacerations presenting with bioburden > 10^5 CFU/gram are associated with increased risk of wound infection[31]. Tri-Solfen studies have demonstrated *in-vitro* antiseptic efficacy, and *in-vivo* efficacy to lower wound bioburden below such levels within 1 minute and up to 4 hours following application (unpublished data). A reduced incidence of bacterial peritonitis following piglet castration has also been observed in treated animals[13].

Regarding efficacy, the potential for similar efficacy in humans as observed in animals can be attributed to the consistent mechanism of action of local anaesthetic agents across mammalian species, due to the similarity of the mammalian nervous system. The selection of local anaesthetics in Tri-Solfen was informed by data from both human and animal studies identifying that a combination of lidocaine, bupivacaine and adrenaline was likely to provide an optimal formulation for rapid onset local anaesthesia, with prolonged duration of sensory analgesic effect, particularly applied to vascular or subcutaneous tissues, as may be present in wounds[32,33]. Results from Tri-Solfen trials in livestock showing optimal safety and efficacy for wound anaesthesia using a combination of lidocaine 5% and bupivacaine 0.5%, with adrenaline 1:40,000, thus aligns closely with available data derived from analogous human use. Livestock treated with Tri-Solfen typically experience wound numbing within 30 seconds to 1 minute of application, whether applied to skin lacerations, burns, or directly to mucosal tissue such as the spermatic cord in piglets[4,5,7,8,10,11]. This is consistent with the inclusion of lidocaine 5% with adrenaline in the formulation. Wound analgesic effects are long lasting, albeit with variability, ranging from 2 to 4 hours (following neonatal piglet castration)[10-12] and up to 24 hours (following lamb mulesing)[5]. This is consistent with the inclusion of 0.5% Bupivacaine in the formulation. The variability in duration of effect may be partially explained by different responses to pain in different species. Neonatal piglets for example do not reliably express pain-related behaviour for more than about 30 minutes following castration[34], where-as lambs reliably express pain for 24 hours or more following mulesing[5]. Duration of effect may also be impacted by the vascularity of the wound site and degree of bleeding which may lessen retention of the product at the site. For haemorrhagic wounds (amputation dehorning of cattle is an example) physical measures such as torniquet, vascular clamps or cautery may be needed to control bleeding prior to application of topical anaesthesia, and/or use of impregnated pressure bandaging to retain the formulation at the wound site. Studies are ongoing in this field.

These extensive data, submitted in support of veterinary medicines regulatory approvals to date, confirm that Tri-Solfen may be safely applied to open wounds and effective to mitigate pain, with rapid onset and prolonged effect, suggesting the potential to also be safe and effective to anaesthetise wounds and alleviate pain in humans. These data have provided an extensive pre-clinical database, supporting the initiation of human phase 2 trials, the first of which are now underway in Ukraine, and yielding promising early results.

Conclusion.

Advances in veterinary medicine over the past two decades have shown that topical anaesthesia (specially formulated, with adrenaline) is safe to apply to open wounds, including large, vascular or complex wounds such as seen following surgical husbandry procedures. It is effective to provide rapid onset wound anaesthesia with prolonged sensory analgesia effects. These findings suggest that, similarly formulated topical anaesthesia may also be useful for addressing pain in humans with analogous wounds, particularly where current options are limited or painful. Extensive pre-clinical data from animal studies confirming the safety and efficacy of this application have supported the initiation of phase 2 trials to investigate similar uses in humans.

Conflicts of Interest Statement

Dr Sheil is a founding director and Chief Medical Officer of Medical Ethics Pty Ltd, and subsidiary Animal Ethics Pty Ltd, research and development company responsible for the development of Tri-Solfen topical anaesthetic for use in livestock species.

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